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10/544,259	12/09/2005	Peter Altenschopfer	MARKS0801 (041376-0801)	1348

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FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
TRAN, SUSAN T	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/544,259	ALTENSCHOPFER ET AL.	
	Examiner	Art Unit	
	S. Tran	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 28-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transdermal patch comprising granisetron, does not reasonably provide enablement for a method for the treatment and/or prophylaxis of a patient having, or susceptible to, a condition selected from the group consisting of: pruritus, fibromyalgia and pain associated therewith, migraine, anxiety, cognitive and psychotic disorders, depression, schizophrenia, psychosis in postnatal depression, irritable bowel syndrome, alcoholism, obstructive sleep disturbed breathing, motion sickness, loss of cognitive function, urinary incontinence, dyskinesia, systemic lupus erythematosus, drug-induced pruritus, premature ejaculation, eating disorders, obsessive compulsive disorder, gastric motility disorders, chronic fatigue syndrome, dyspepsia and cocaine dependence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: 1) breadth of the claims; 2) nature of the invention; 3) state of the prior art; 4) amount of direction provided by the inventor; 5) the level of predictability in the art; 6) the existence of working examples; 7) quantity of experimentation needed to

make or use the invention based on the content of the disclosure; and 8)relative skill in the art. All of the factors have been considered with regard to the claims, with the most relevant factors being discussed below:

Breadth of the claims is broad. Claim 32 is directed to a transdermal patch comprising granisetron suitable for the treatment or prophylaxis of about 26 different conditions.

Amount of direction provided by the inventor, and quantity of experimentation needed to use the invention: while the present specification disclosed that the patch of the present invention are suitable for the treatment of any form of nausea and emesis associated with activation of 5-HT_3 receptors, such as with cancer therapy (page 9, 4th paragraph), the specification fails to describe how to precisely achieve the claimed method for the treatment and/or prophylaxis of a patient having multitudes condition such as: pruritus, fibromyalgia and pain associated therewith, migraine, anxiety, cognitive and psychotic disorders, depression, schizophrenia, psychosis in postnatal depression, irritable bowel syndrome, alcoholism, obstructive sleep disturbed breathing, motion sickness, loss of cognitive function, urinary incontinence, dyskinesia, systemic lupus erythematosus, drug-induced pruritus, premature ejaculation, eating disorders, obsessive compulsive disorder, gastric motility disorders, chronic fatigue syndrome, dyspepsia and cocaine dependence. Let alone the patch recited in claim 1 without any specific amount of active agent.

There is no evidence from the present specification showing that applying a granisetron patch of the present invention can treat patient with condition such as

schizophrenia, alcoholism, chronic fatigue syndrome, or depression. There is no evidence of correlation between these disorders, much less, 26 different disorders using one same patch of granisetron. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to make and/or use the claimed transdermal patch without undue experimentation.

As such, the practitioner would turn to trial and error experimentation in order to compose the claimed composition for the treatment of condition such as: pruritus, fibromyalgia and pain associated therewith, migraine, anxiety, cognitive and psychotic disorders, depression, schizophrenia, psychosis in postnatal depression, irritable bowel syndrome, alcoholism, obstructive sleep disturbed breathing, motion sickness, loss of cognitive function, urinary incontinence, dyskinesia, systemic lupus erythematosus, drug-induced pruritus, premature ejaculation, eating disorders, obsessive compulsive disorder, gastric motility disorders, chronic fatigue syndrome, dyspepsia and cocaine dependence, without guidance from the specification or the prior art.

The relative skill of those in the art: the skill of one of ordinary skill in the art is very high, e.g., Ph.D. and M.D. level technology.

Claim Rejections - 35 USC § 103

Claims 1-26, 28-31, 33 and 34 rejected under 35 U.S.C. 103(a) as being unpatentable over Effing et al. WO 98/53815 A1, in view of Miranda et al. US 5,656,286 or Horn et al. US 3,269,994.

Effing teaches a transdermal drug delivery device or a pressure sensitive skin adhesive device comprising an adhesive layer containing: 1) a copolymer of one or more A monomers and one or more B monomers, and 2) a therapeutically effective amount of granisetron as an active agent (abstract; page 2, lines 14-28; and claims 1 & 11). A monomers include n-butyl, and 2-ethylhexyl acrylates or methacrylates (page 4, 2nd paragraph; and claim 10). Active agent presents in the device ranges from 4-15% (page 5, lines 28-29). Effing further teaches the device has a surface area of about 15 cm^2 to about 60 cm^2 (page 7, lines 20-22). The device comprising granisetron is useful for the treatment of emesis and/or nausea during chemotherapy (abstract; page 1, lines 23-27; page 3, lines 1-5; and page 7, lines 23-29). The device shows stability at storage conditions under 25°C and 40°C after 4 weeks (examples 1 & 2).

Effing does not expressly teach the claimed transdermal patch with specific amounts of monomers.

Miranda teaches a transdermal composition comprising an adhesive layer comprising from about 2% to about 95% polyacrylate polymer (abstract; column 7, lines 20-29; column 9, lines 34-59; and column 10, lines 37-45). Polyacrylate polymer comprises at least 50% by weight of an acrylate or alkyl acrylate monomer, and from 0-20% of a functional monomer copolymerizable with the acrylate (column 10, lines 46-57). Acrylate monomer includes butyl acrylate or 2-ethylhexyl acrylate. Functional monomer includes acrylic acid or methacrylic acid such as hydroxyethyl meth(acrylate), and hydroxypropyl meth(acrylate) (column 10, lines 58 through column 11, lines 1-7). The adhesive layer further comprises from about 0.1% to about 50% drug including an

antinauseant agent such as granisetron (column 10, lines 13-20; column 22, lines 38-42; and claim 62).

Horn teaches an adhesive coating comprising from about 70% to about 97% Group I monomer, and from about 30% to about 3% Group II monomer (column 2, lines 67 through column 3, lines 1-3). Group I monomer includes butyl acrylate or 2-ethylhexyl acrylate (column 2, lines 32-39). Group II monomer includes hydroxymethyl acrylate, hydroxyethyl acrylate, hydroxypropyl acrylate, and corresponding esters of methacrylic acid in place of the acrylic acid esters thereof (column 2, lines 57-65).

Thus, it would have been obvious to one of ordinary skill in the art to optimize the transdermal composition of Effing in view of the teachings of Miranda or Horn to obtain the claimed invention. This is because Miranda teaches a transdermal composition that can prevent crystallization of the drug (stability) without effecting the rate of drug delivery from the composition, because Miranda teaches a transdermal composition suitable for a wide variety of drugs including granisetron, because Horn teaches a storage stable adhesive patch useful for a wide variety of purples (column 1, lines 17-68), and because Effing teaches the desirability for obtaining a stable transdermal composition suitable for granisetron.

It is noted that the cited references do not teach the claimed properties, such as the release profiles, as well as the storage stability. However, the burden is shifted to applicant to show that the adhesive compositions taught by Miranda or Horn do not exhibit the claimed properties, because Miranda teaches the same transdermal composition using the same acrylic adhesive and in the claimed amount.

Claims 1-26 and 28-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seo et al. WO 00/47208 A1, in view of Miranda et al. US 5,656,286 or Horn et al. US 3,269,994.

Seo teaches a transdermal composition comprising an anti-vomiting agent such as granisetron (abstract; and pages 5-6).

It is noted that Seo does not expressly teach the claimed transdermal patch with specific amounts of monomers.

Miranda teaches a transdermal composition comprising an adhesive layer comprising from about 2% to about 95% polyacrylate polymer (abstract; column 7, lines 20-29; column 9, lines 34-59; and column 10, lines 37-45). Polyacrylate polymer comprising at least 50% by weight of an acrylate or alkyl acrylate monomer, and from 0-20% of a functional monomer copolymerizable with the acrylate (column 10, lines 46-57). Acrylate monomer includes butyl acrylate or 2-ethylhexyl acrylate. Functional monomer includes acrylic acid or methacrylic acid such as hydroxyethyl meth(acrylate), and hydroxypropyl meth(acrylate) (column 10, lines 58 through column 11, lines 1-7). The adhesive layer further comprises from about 0.1% to about 50% drug including an antinauseant agent such as granisetron (column 10, lines 13-20; column 22, lines 38-42; and claim 62).

Horn teaches an adhesive coating comprising from about 70% to about 97% Group I monomer, and from about 30% to about 3% Group II monomer (column 2, lines 67 through column 3, lines 1-3). Group I monomer includes butyl acrylate or 2-ethylhexyl acrylate (column 2, lines 32-39). Group II monomer includes hydroxymethyl

acrylate, hydroxyethyl acrylate, hydroxypropyl acrylate, and corresponding esters of methacrylic acid in place of the acrylic acid esters thereof (column 2, lines 57-65).

Thus, it would have been obvious to one of ordinary skill in the art to optimize the transdermal composition of Seo in view of the teachings of Miranda or Horn to obtain the claimed invention. This is because Miranda teaches a transdermal composition that can prevent crystallization of the drug (increases flux, and prevents skin irritation) without effecting the rate of drug delivery from the composition (abstract; and column 2, lines 19-23), because Miranda teaches a transdermal composition suitable for a wide variety of drugs including granisetron, because Horn teaches a storage stable adhesive patch useful for a wide variety of purples (column 1, lines 17-68), and because Seo teaches the desirability for obtaining a transdermal composition suitable for delivering granisetron over a period of day or more without skin irritation.

It is noted that the cited references do not teach the claimed properties, such as the release profiles, as well as the storage stability. However, the burden is shifted to applicant to show that the adhesive compositions taught by Miranda or Horn do not exhibit the claimed properties, because Miranda teaches the same transdermal composition using the same acrylic adhesive and in the claimed amount.

Response to Arguments

Applicant's arguments filed 03/20/09 have been fully considered but they are not persuasive.

Applicant argues that contrary to the Examiner's assertion, one skilled in the art has been provided with more than enough information to use the present invention commensurate in scope with the claims. As readily recognized by one of skill in the art, each of the indications contemplated for treatment by the method of claim 32 have all been demonstrated to be dependent on the 5-HT3 receptor. Taken together with the fact that granisetron, the active component delivered by the adhesive patch of the invention, specifically targets the 5-HT3 receptor (and the showing herein that the adhesive patch of the invention has surprisingly good drug release properties and surprisingly good skin flux properties), one of skill in the art would have every reason to expect the adhesive patch of the invention to be useful for the treatment of each of the indications contemplated by the method of claim 32.

However, in response to applicant's argument that *as readily recognized by one of skill in the art, each of the indications contemplated for treatment by the method of claim 32 have all been demonstrated to be dependent on the 5-HT3 receptor*, it is noted that claim 32 is not directed to a method for the treatment of condition dependent on the 5-HT_3 receptor. To the contrary, the present teaches the patches of the present invention are useful in the treatment of emesis associated with chemotherapy, Such as nausea and vomiting. There is no teaching in the present specification how chemotherapy related to the 26 disorders recited in claim 32. Moreover, there is no

evidence from the present specification showing the relationship/correlation of the 26 conditions recited in claim 32. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to make and use the claimed transdermal patch for the treatment of 26 different disorders without undue experimentation. Accordingly, the 112, 1st paragraph rejection is maintained.

Applicant argues that in contrast to that which is required by the present claims, Effing et al. clearly teach against the use of an acrylic adhesive containing non-acidic hydroxyl moieties in combination with tropisetron or granisetron. Thus, to the extent that the Office Action relies on the Effing et al. reference, it is incumbent upon the Examiner to consider the reference as a whole, for all that it teaches, not just that which is convenient for the Examiner's purposes. A fair reading of the reference, when taken as a whole, teaches both the interchangeability of tropisetron and granisetron, and the undesirability of using hydroxy-containing monomers (such as 2-hydroxyethylacrylate (HEA)) in the preparation of an adhesive patch containing tropisetron or granisetron.

However, in response to applicant's argument that Effing does not teach the use of an acrylic adhesive containing non-acidic hydroxyl moieties, applicant's attention is called to page 4, 2nd paragraph; and claim 10, for the teaching of monomers include n-butyl, and 2-ethylhexyl acrylates or methacrylates. Further, Effing is cited in view of Miranda or Horn. The secondary references teach the use of non-acidic hydroxyl moieties in an acrylic adhesive composition is well known in the art.

In response to applicant's arguments with respect to Miranda and Horn, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Horn and Miranda are cited solely for the teachings of well a known transdermal system in the art that comprises the claimed acrylic adhesive composition.

Applicant argues that Effing et al.'s failure to recognize any significant structural and/or functional differences between tropisetron and granisetron, the Effing et al. teaching is directed to adhesive patches containing either tropisetron or granisetron. As previously noted (and as discussed at the personal interview), throughout the Effing et al. disclosure, it is suggested that these two compounds are substantially similar both structurally and functionally (see, for example, page 1, line 23-page 2, line 2 of Effing et al., which suggests the interchangeability of these compounds). Indeed, as previously noted, virtually every reference to active drug in the Effing et al. specification is made in the alternative. There are only two exceptions throughout the Effing et al. specification where tropisetron and granisetron are not mentioned in the same clause, i.e., (1) in the background (at page 2, line 10) where "ondansetron and granisetron" are suggested to be interchangeable); and (2) in the Examples, which deal only with tropisetron; however, based on the consistent indication throughout the Effing et al. specification

that tropisetron and granisetron are substantially interchangeable, there is no reason (absent improper reliance on Applicants' disclosure) why one of skill in the art would expect granisetron to perform any differently than tropisetron.

In response to applicant's arguments, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Moreover, a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). In the present case, Effing suggests the desirability for preparing a transdermal patch comprising active agent such as tropisetron or granisetron. Effing is cited in view of secondary references such as Miranda and Horn, for the teaching of well known transdermal compositions useful in the art and suitable for a wide variety of drugs including granisetron.

Applicant argues that while Seo et al. make reference to a "matrix" patch, it is clear that Seo et al. do not envisage using "matrix" patches as that term is commonly used in the art. Instead, Seo et al. misleadingly use the term "matrix" to refer to the filler in the reservoir. In the art, a reservoir patch is what Seo et al. refer to as a matrix patch (and a matrix patch (as that term is consistently used in the art) is referred to as an “adhesive matrix patch”). This is clearly shown by Fig. 3 of Seo et al.: Fig. 3 shows an

embodiment of the monolithic matrix [reservoir] patch of the present invention, which comprises an impervious protective layer(31), a reservoir layer(35), an adhesive layer(33) and a release strip(34). See page 10 of Seo et al. (emphasis added). The above-quoted passage clearly demonstrates that Seo et al. does not use "matrix" in the accepted manner recognized in patch technology. Further evidence that Seo et al. do not relate to matrix patches as contemplated by the present claims is found at p.9, 11.2-4, where it is stated that: An adhesive matrix patch, another form of patch, may not be suitably employed in the present invention because it can carry only limited amounts of an anti-vomiting agent and a soluble skin penetration enhancer in its adhesive layer." (Emphasis added).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., matrix patch, or an adhesive matrix patch, another form of patch, may not be suitably employed in the present invention because it can carry only limited amounts of an anti-vomiting agent and a soluble skin penetration enhancer in its adhesive layer) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that the Seo et al. "matrix" contains 20-80% organic solvent, 1 - 50% PE and 15 - 80% water. In contrast, the adhesive patches of the present invention require no organic solvent, which can lead to skin irritation.

However, in response to applicant's argument, the use of the transitional term "comprising" in the preamble of the claims is noted. The term "comprising" which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., > Mars Inc. v. H.J. Heinz Co., 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term comprising,' the terms containing' and mixture' are open-ended.").< Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

For the above reasons, the 103(a) rejections of record are maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to S. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 8:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. Tran/
Primary Examiner, Art Unit 1615